J. Chem. Research (S),
1998, 400–401†

Microwave Enhanced Hydrogenation Reactions using Solid Hydrogen, Deuterium and Tritium Donors†

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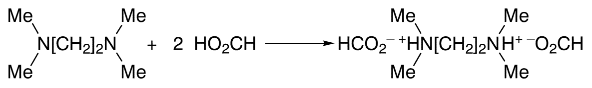
Microwave enhanced hydrogenation reactions in which $H_2/D_2/T_2$ gases are replaced by various formates proceed very rapidly; the pattern of labelling can be easily modified and the advantages are particularly noteworthy in the case of tritium where problems associated with handling T_2 gas are avoided.

Hydrogenation using H_2 gas is one of the most important reactions in organic chemistry.[1] In addition replacement of H_2 with D_2 or T_2 constitutes one of the most widely used methods for preparing deuterium[2] and tritium[3] labelled compounds, which themselves find wide application in the life sciences.[4] Unfortunately all three gases are sparingly soluble in many common solvents with the result that the catalysed reactions, be they heterogeneous or homogeneous, are frequently very slow. As tritium is radioactive this is an additional concern. Consequently our thoughts have turned to the use of solid hydrogen, deuterium and tritium donor sources and here we report our preliminary findings using both thermal and microwave enhanced conditions.

Catalytic hydrogen transfer[5] is a special kind of hydrogenation in which the compound to be hydrogenated is heated in the presence of a solvent, catalyst and a hydrogen donor. Amongst the latter we chose the formates, usually the potassium, sodium or ammonium salts, but as they can only donate one hydrogen (the other usually comes from the small concentration of protic solvent present in the reaction mixture) we also synthesized the diformic acid salt of tetramethylethylenediamine (TMEDA):



$$Me_2N[CH_2]_2NMe_2 + 2\ HO_2CH \longrightarrow HCO_2^{-}\,{}^{+}HNMe_2[CH_2]_2NMe_2H^{+}\,{}^{-}O_2CH$$

Deuteriated formates are commercially available whilst tritiated potassium formate was prepared at high specific activity (2.5 Ci $mmol^{-1}$) by a metal catalysed hydrogen–tritium exchange procedure using T_2 gas.

Since the first reports[6,7] of the benefits of microwaves in synthetic organic chemistry appeared the field has seen considerable growth but there have been very few applications in the labelled compounds area, the main focus being on radiopharmaceuticals[8,9] containing the short-lived positron emitters ^{11}C and ^{18}F.

Microwave energy transfer is by dielectric loss and not by conduction or convection so that solvents with high dielectric constants such as dimethyl sulfoxide, dimethylformamide, water and some alcohols are favoured. The results (Fig. 1) show that with ammonium formate as a donor, the hydrogenation of α-methylcinnamic acid under thermal conditions takes some 2 h at 50 °C and 30 min at 100 °C to go to completion whereas under microwave conditions it is complete in less than 5 min. Furthermore more sterically hindered alkenes such as α-phenylcinnamic acid which are reduced with extreme difficulty when using H_2 gas and Wilkinson's catalyst are easily reduced under microwave enhanced conditions.

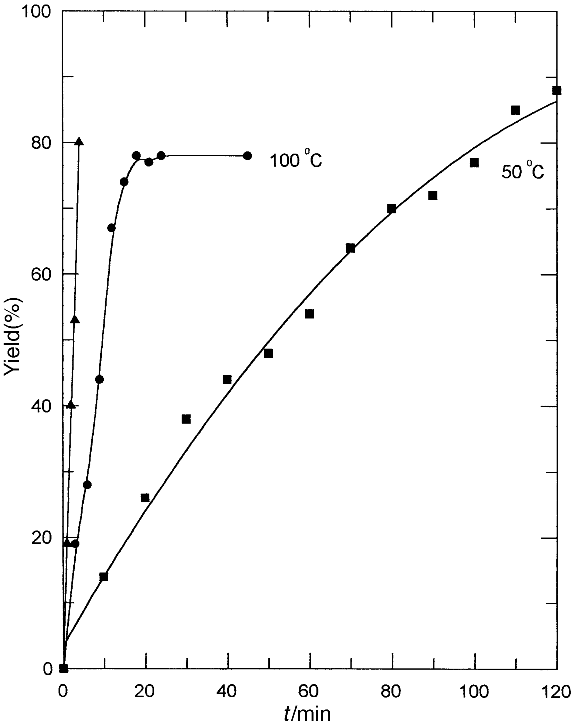


Fig. 1 Hydrogenation of α-methylcinnamic acid: ■ 50 °C, thermal conditions; ● 100 °C, thermal conditions; ▲ microwave irradiation

A further feature of the solid donor work is that it gives rise to the possibility of different labelling patterns. Whilst it is customary in the homogeneous hydrogenation of alkenes when using D_2 gas and Wilkinson's catalyst to obtain very even addition across the double bond thus:

$$RCH{=}CHR' + D_2 \rightarrow RCHD{-}CHDR'$$

with the formates there are three possibilities depending on the combination used: $H_2O + DCO_2^-$, $D_2O + HCO_2^-$, $D_2O + DCO_2^-$ (or DCO_2D salt of TMEDA on its own). These expectations are borne out in the results obtained (Fig. 2) for the hydrogenation of cinnamic acid.

Whilst the advantages of the procedure (no gas line required, rapid reactions, sterically hindered compounds hydrogenated, labelling patterns varied) for both hydrogen and deuterium are clear it is the tritium work that will benefit most. The tritium is kept as a solid, which can be safely stored for long periods of time, and is easier to handle than T_2 gas. Furthermore considerably less radio-

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

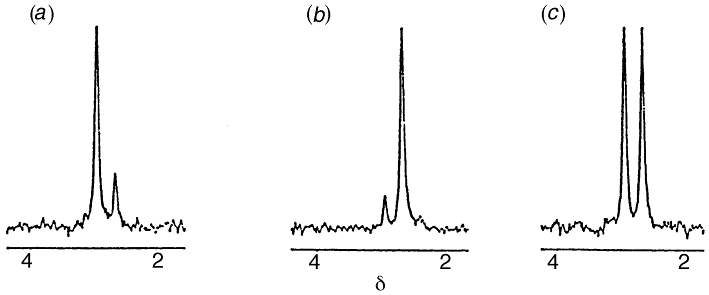

Fig. 2 ^2H NMR (^1H decoupled) spectra of dihydrocinnamic acid formed using (*a*) HCO_2K and D_2O, (*b*) DCO_2K and H_2O and (*c*) DCO_2K and D_2O

active waste is produced by using stoichiometric quantities of tritiated formates rather than the excess of T_2 gas which is usually employed for complete reduction.

Experimental

NMR spectra (^1H, ^2H, ^3H) were recorded on a Bruker AC-300E spectrometer in the customary manner.

Preparation of Formic Acid/TMEDA Salt.—TMEDA (8 ml) was added to a 50 ml round bottom flask, which was cooled to 0 °C in an ice-bath. Formic acid (5 g) was added over the course of a minute whilst the reaction mixture was vigorously stirred. The white solid which precipitated after 5 min was separated off and dried under vacuum. [$^2H_2$]Formic acid/TMEDA salt: δ_H (300 MHz, $CDCl_3$) 2.98 [4 H, s, $(CH_2)_2$], 2.58 (12 H, s, CH_3); δ_D (46 MHz, $CHCl_3$) 12.65 (1 H, s, CO_2D), 8.43 (1 H, s, CD).

General Procedure for Reactions using Labelled Formate Salts and/or Water.—The substrate (25–100 mg), formate (20–100 mg) and [$Rh(PPh_3)_3Cl$] (5–15 mg) were weighed into a 25 ml pear shaped flask to which dimethyl sulfoxide (0.5 ml) and water (50–200 μl) were added. The flask was fitted with a modified thermometer adapter and septum seal so that it could easily be flushed with N_2 and then evacuated prior to inserting in the thermostat. On completion of the reaction, water (10 ml) was added and the product(s) extracted with chloroform (5 ml). The solution was further washed with water before being dried over anhydrous magnesium sulfate and finally passed down a small silica column to remove the catalyst; the solvent was removed by passing a stream of N_2 over its surface.

Received, 19th February 1998; Accepted, 1st April 1998
Paper E/8/02040J

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